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Balloon Photodynamic Therapy of Esophageal Cancer: Effect of Increasing Balloon Size

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Background and Objective: **Photodynamic therapy is currently being used to treat various malignancies including esophageal cancer. The effect of photodynamic therapy depends upon the concentration of photosensitizing drug, light energy delivered to tissue, and the presence of oxygen in the targeted tissue. We have found that an esophageal centering balloon improves light delivery to esophageal mucosa. However, balloon pressure on esophageal mucosa could possibly reduce mucosal blood flow and oxygenation, therefore reducing the effect of photodynamic therapy. This study was conducted to investigate the effect of balloon pressure on the esophageal wall during photodynamic therapy in the canine esophageal model.**

Study Design/Materials and Methods: **Studies were performed in the canine esophagus of ten animals to investigate whether increasing the size of the centering balloon, and hence the pressure on esophageal mucosa, would alter the tissue effect of PDT. Porfimer sodium 4 mg/Kg was administered and 630 nm light was delivered via a 1 cm diffuser located in the center of a 360° 2 cm windowed balloon. Mucosal light measurements were made to ascertain equivalent mucosal light dosing of ~25 J/cm^2. Endoscopic and necropsy findings obtained following photodynamic therapy with 25 mm, 33 mm, and 35 mm balloons were compared.**

Results: **In larger dogs (groups A and B), increasing the size of the esophageal centering balloon from a 25–33 mm size did not result in an overly tight fit nor was the increase associated with significant change in the PDT effect. In contrast, increasing the balloon size to 35 mm in smaller dogs (group C) resulted in a tight fit of the balloon in the esophagus and in significant reduction in the PDT effect on mucosal damage when mucosal equivalent light dose was administered during photodynamic therapy in the canine esophageal model.**

Conclusion: **Increasing centering balloon size resulted in reduced tissue damage when mucosal equivalent light dose was administered during photodynamic therapy in the canine esophageal model. Proper sizing of centering balloons will be necessary for balloon PDT of esophageal mucosal dysplasia or cancer in humans.** © 1996 Wiley-Liss, Inc.

Key words: photodynamic therapy, esophageal cancer, balloon

INTRODUCTION

Photodynamic therapy (PDT) [1–3] involves injecting a light-sensitive drug that selectively concentrates in malignant tissue. When activated by a light of proper wavelength and power, the

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TABLE 1. Results of Esophageal PDT Using Centering Balloons of Different Sizes

GROUP	n	Treated sites	Average fluence J/cm^{2a}	Balloon diameter (mm)	Endosc/histol damage[b]
A	6	12	26.34	25	3–4+
B	2	4	24.34	33	3–4+
C	2	4	25.09	35	0–1+

[a]J/cm^2 = joules/centimeter^2.
[b]Endosc = endoscopic; histol = histologic.

drug produces the cytotoxic agent, singlet oxygen, which leads to destruction of the malignant tissue. PDT is an experimental treatment at this time. Phase III clinical trials in patients with advanced esophageal cancer have been completed.

Previous studies have documented the effectiveness of a centering balloon in delivering circumferential and uniform light to the esophagus during PDT [4–6]. Further balloon refinements led to the development of a 180° or 360° windowed balloon that allowed targeted light delivery to esophageal mucosa during PDT [7]. As part of an on-going program to develop improved PDT delivery systems for esophageal cancer, this report analyzes the effect of increasing balloon size on altering PDT response in the canine esophagus.

MATERIALS AND METHODS

The canine esophagus was used as a model for in vivo testing of the centering balloons. The use of animals for the study was approved by the Animal Care and Concern Committee of the College of Veterinary Medicine, University of Tennessee. All dogs weighed between 18–23 kg except for animals in group C (Table 1), which by design used smaller animals weighing 12–13 kg. Porfimer sodium (Quadra Logic Technologies, Vancouver, B.C., Canada) was reconstituted with 5% dextrose to a final concentration of 2.5 mg/ml and injected intravenously at a dose of 4.0 mg/kg, a dose previously shown to produce damage in the canine esophageal model [4–6].

The dogs were kept indoors for the duration of the study. Animals were anesthetized 40–50 hours later with atropine sulfate 0.75 mg and acepromazine maleate 3 mg. Intravenous thiamyl sodium was administered 1 hour later. Anesthesia was maintained using isofluorane inhalation. Oxygen saturation was determined using a pulse oximeter with the probe placed on the tongue. Upper gastrointestinal endoscopy was performed with the Fujinon EVG-CT videoendoscope. The gastroesophageal (GE) junction was located and measured from the canine incisors. Areas treated with the 2 cm windowed balloon were designated at 5–7 cm and 15–17 cm proximal to the GE junction. The deflated balloon was inserted to the appropriate level and positioned under endoscopic guidance and inflated. Once the position of the balloon had been endoscopically verified, the balloon shaft was taped in place and the endoscope was removed. The laser fiber probe with a 1 cm diffuser tip was then passed into the center of the balloon. Treated sites received ~25 J/cm^2 to the mucosa. The dogs were endoscoped 48 hours later to document endoscopic damage and were then euthanized. Endoscopic abnormalities were graded as: normal = 0; edema, focal petechiae = 1+; diffuse petechial hemorrhage = 2+; shallow ulceration = 3+; and hemorrhagic necrosis = 4+. Histologic abnormalities were graded as: normal = 0; edema and mild interstitial hemorrhage = 1+; marked interstitial hemorrhage = 2+; vascular degeneration = 3+, and ulceration with necrosis = 4+. Necropsy studies of the esophagus and adjacent organs were performed.

The centering balloon has been described previously [4–7]. It consisted of two major parts: (1) a semiflexible tube containing two small concentric vinyl tubes, and (2) an inflatable cylindrical balloon attached to the distal end. The inner tube used to introduce the cylindrical diffuser into the balloon was optically clear and had an inside diameter large enough to allow passage of the cylindrical diffuser. A removable stylet was placed inside this inner tube to increase the stiffness during passage into the esophagus. The distal end of the inner tube was sealed. The inner tube allowed use of commercially available cylindrical diffusers for photodynamic therapy. The second inner tube was used for inflation and deflation of the balloon and terminated at the proximal end of the balloon.

The overall length of the cylindrical balloon was 60 mm with an outside diameter of 25, 33, or 35 mm when fully inflated to 0.1 psi. The balloons were maintained at 0.1 psi during the studies.

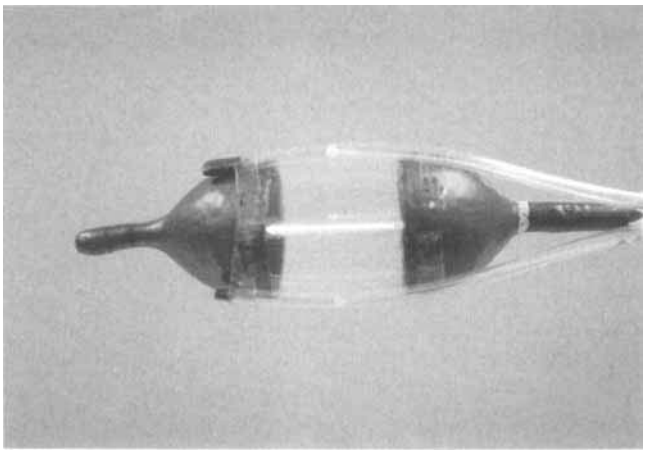

Fig. 1. Esophageal centering balloon with a 360° window. Two of the three isotropic probes placed 120° from each other are seen attached to the outside of the balloon. The diffuser is seen in the center of the balloon window.

The balloon was tapered at both ends providing an effective cylindrical length of 35 mm. A 360° 2 cm balloon window was prepared as described previously [7]. The balloon was constructed from an optically clear polyurethane membrane with thickness of ~0.11 mm (Datascope Corp., Paramus, NJ). Mucosal light measurements were obtained during therapy using three isotropic probes (Model 2818, PDT Systems, Santa Barbara, CA) that were inserted in small polyvinyl tubes taped to the outside of the balloon at 120° from each other (Fig. 1). The diameter of the spherical tip of these probes was ~1.8 mm. The tips of the isotropic probes were in the same plane as the center of the 1.0 cm cylindrical diffuser inside the inner tube. The collected light from the probes was measured in milliwatts per square centimeter using a single channel in vivo light dosimeter (Model 2710, PDT Systems) calibrated at 630 nm. The readings were corrected for variation in probe response.

Treatment variables consisted of three balloon sizes (25, 33, and 35 mm diameter) and variable light exposure times at 300 J/cm diffuser to achieve equivalent *mucosal* light doses of 25 J/cm^2. Treatment with the 35 mm balloon was performed in two smaller dogs (12.3 and 13.2 kg, Group C) to achieve greater luminal distention, mucosal thinning, and a presumed reduction in mucosal blood flow.

An argon-pumped dye-laser, Model 2016/375B (Spectra-Physics, Mountain View, CA) tuned at 630 nm was used as the light source. The wavelength was verified using an optical multichannel analyzer system, OMA III (EG&G Princeton Applied Research, Princeton, NJ). The light was focused into a 200-μm extension fiber (Model 5220, PDT Systems). A 400-μm 1.0 cm cylindrical diffuser (Model 4410, PDT Systems) was attached to the extension fiber. The power from the cylindrical diffuser was measured using an integrating spherical power meter (Model 2010, PDT Systems) and was adjusted to 400 mW/cm. The power meter was calibrated at 630 nm.

RESULTS

Endoscopic observation of the inflated balloons showed no significant light diffusion above the 33 mm and 35 mm balloons except for minimal light tracking along the measuring probe tubes attached to the outside of the balloon. The 25 mm balloons demonstrated some light leakage from the windowed area during inspiration. The 25 mm balloon fit loosely in the esophageal lumen but flattened the folds sufficiently. The 33 mm and 35 mm balloons were observed to fit snugly against the esophageal wall. The inflated 33 mm and 35 mm balloons could be moved only with moderate pulling on the balloon shaft, whereas the 25 mm balloons could be moved by mildly pulling on the balloon shaft.

The 360° balloon window resulted in mucosal injury limited to the mucosa exposed to light. Severity of PDT damage visualized endoscopically at 48 hours paralleled histologic damage in all dogs. PDT injury was mild where the light measuring tubes protected the mucosa. Oxygen saturation as measured by pulse oximetry was maintained in the 96–97% range. In one of the smaller dogs, saturation dropped to 86% transiently.

Increasing balloon size resulted in less injury. When equivalent mucosal light doses were delivered in the larger dogs (Groups A, B), PDT injury was moderate to marked (3–4+) with the 25 mm and 33 mm balloons. When the 33 mm balloon was used in the smaller dogs (Group C) to increase the pressure on the esophageal wall, endoscopic and histologic injury was minimal (0–1+) in the four treated areas.

DISCUSSION

Human treatment with PDT consists of an IV injection of 2.0 mg/kg of porfimer sodium followed by endoscopic delivery of laser light 40–50 hours later. Light delivery for esophageal cancer consists of passing a fiberoptic probe with a cylin-

drical diffuser on its end through the biopsy channel of an endoscope. The diffuser is positioned to illuminate the esophageal tumor superficially or interstitially. The dose of light delivered is 300 J/cm length of diffuser at a power density of 400 mW per cm. Light doses reaching the mucosal surface using this system have been determined theoretically and not actually measured. The effect of PDT on tissue is determined by drug concentration in the tissue, the amount of light of proper wavelength delivered to the tissue and tissue oxygen concentration.

When planning photodynamic therapy of esophageal tumors, it is assumed that the esophagus is a hollow tubular organ and that the cylindrical diffuser is placed in the center of the lumen. In reality, proper placement and maintenance of a cylindrical diffuser in the center of the esophageal lumen are difficult. Since the biopsy channel of GI endoscopes is positioned at the side of the instrument tip, the diffuser exits the scope eccentrically. During PDT, this design results in the deposition of more light to one side of the esophagus. In addition, respiratory movement and esophageal motility prevent uniform and precise illumination of small esophageal lesions. In far advanced circumferential cancers, the off-center location of the probe and the effects of respiratory and esophageal motility movements are less critical. In contrast, during PDT of early esophageal cancer [8–9], the positioning and stabilization of the probe become important considerations in the delivery of PDT.

The major role of PDT in esophageal disease likely will be for the treatment of early malignant and premalignant esophageal lesions. However, due to the instrument and treatment variables mentioned above, a windowed centering balloon has been developed to improve the delivery of light to the esophageal *mucosa* [7]. Advantages of the balloon include the ability to deliver circumferential, uniform, and predictable light to a desired area. The balloon also reduces the effects of esophageal motility and cardiac or respiratory movement on the delivery of quantifiable light to a targeted area of the esophagus. Concern exists, however, that balloon pressure on the esophageal wall might reduce the PDT effect by reducing mucosal blood flow, resulting in less mucosal oxygenation and therefore a decreased PDT effect.

Indeed, our results demonstrate that increasing balloon size results in less mucosal and tissue injury. PDT with the 25 mm balloon resulted in moderate to marked esophageal injury. In these dogs, the balloon position could be changed with mild tugging on the balloon shaft, indicating the balloon was not pressed tightly against the esophageal wall. With equivalent mucosal light dosing, endoscopic and histologic effects were also moderate to marked with the 33 mm balloon. In these dogs, endoscopic observations revealed the balloons to be snug but not overly tight. The inflated 33 mm balloons could be moved short distances with moderate tugging on the balloon shaft, suggesting the inflated balloons fit snugly but were not overly tight.

In order to achieve a relatively greater balloon distention of the esophageal lumen, smaller dogs weighing 12–13 Kg (Group C) were studied with the 35 mm balloon with the intent of achieving a greater degree of luminal distention, mucosal thinning, and presumably some reduction of blood flow and tissue oxygenation. Moderate pulling on the shaft of the inflated 35 mm balloon did not change its position in these dogs, suggesting a tight fit. Endoscopic observations supported this finding. Although the physiologic effects of the large balloon on luminal distention and mucosal blood flow could not be measured directly, the endoscopic and histologic injury following PDT with equivalent mucosal light dose was much less in the smaller dogs than in the larger animals. In contrast to the moderate to marked injury in the larger dogs, minimal if any injury was seen in areas treated in the smaller dogs.

These observations present evidence that excessive pressure on the esophageal wall results in less PDT effect. Other investigators have determined that hypoxia reduces the effect of PDT in cell cultures and in mice [10–12]. Thus a possible mechanism for the reduced PDT effect seen with increasing esophageal wall pressure may be that stretching and thinning the esophageal wall reduces blood flow, which in turn results in reduced tissue oxygenation and therefore less PDT effect.

This observation has clinical importance. The centering balloon for esophageal PDT must not be too large. Studies are currently in progress to develop and test the proper balloon size in humans.

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